19-0056 Doc 5
19-0059 Doc 5

Antimalarial Drug Resistance

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Case Management Technical Working Group
PMI/CDC

January 2018

Center for Global Health
Division of Parasitic Diseases and Malaria

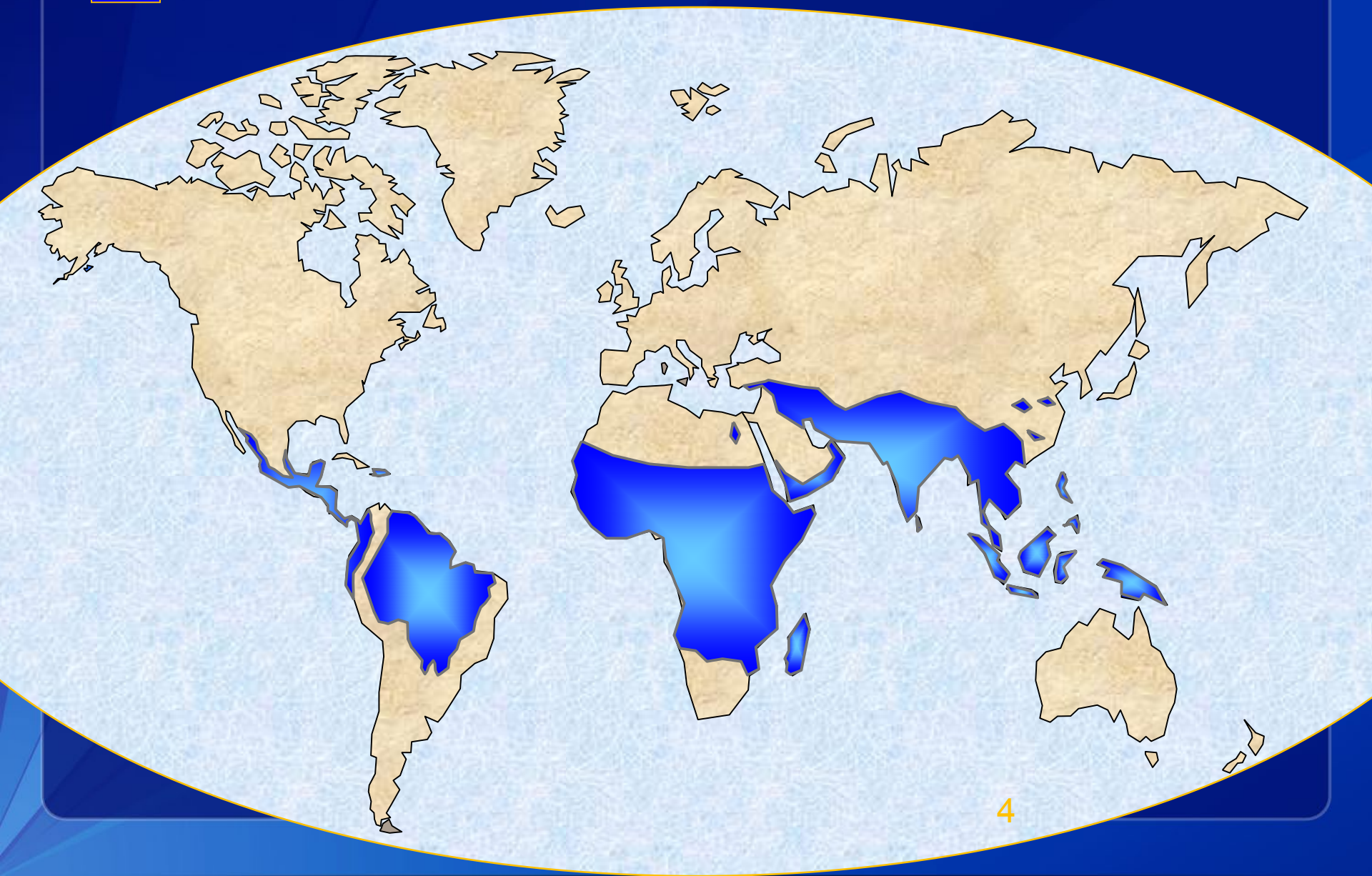
Lecture Outline

- A little history
- Definitions and concepts
- Recent literature review
- Therapeutic efficacy studies
- Your role in this

A LITTLE HISTORY

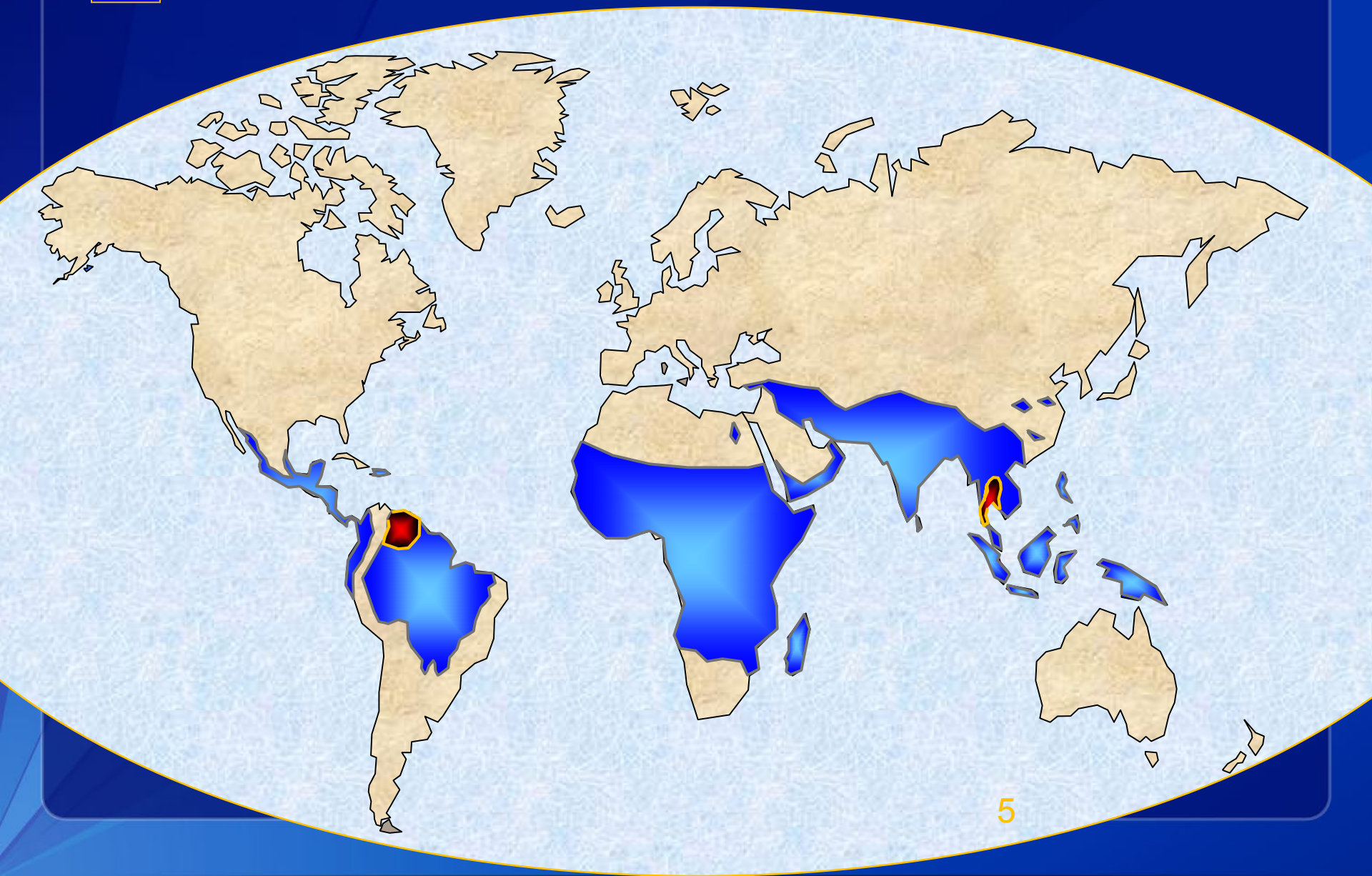
Distribution of Chloroquine Resistant *P. falciparum* circa 1950

Distribution of Malaria



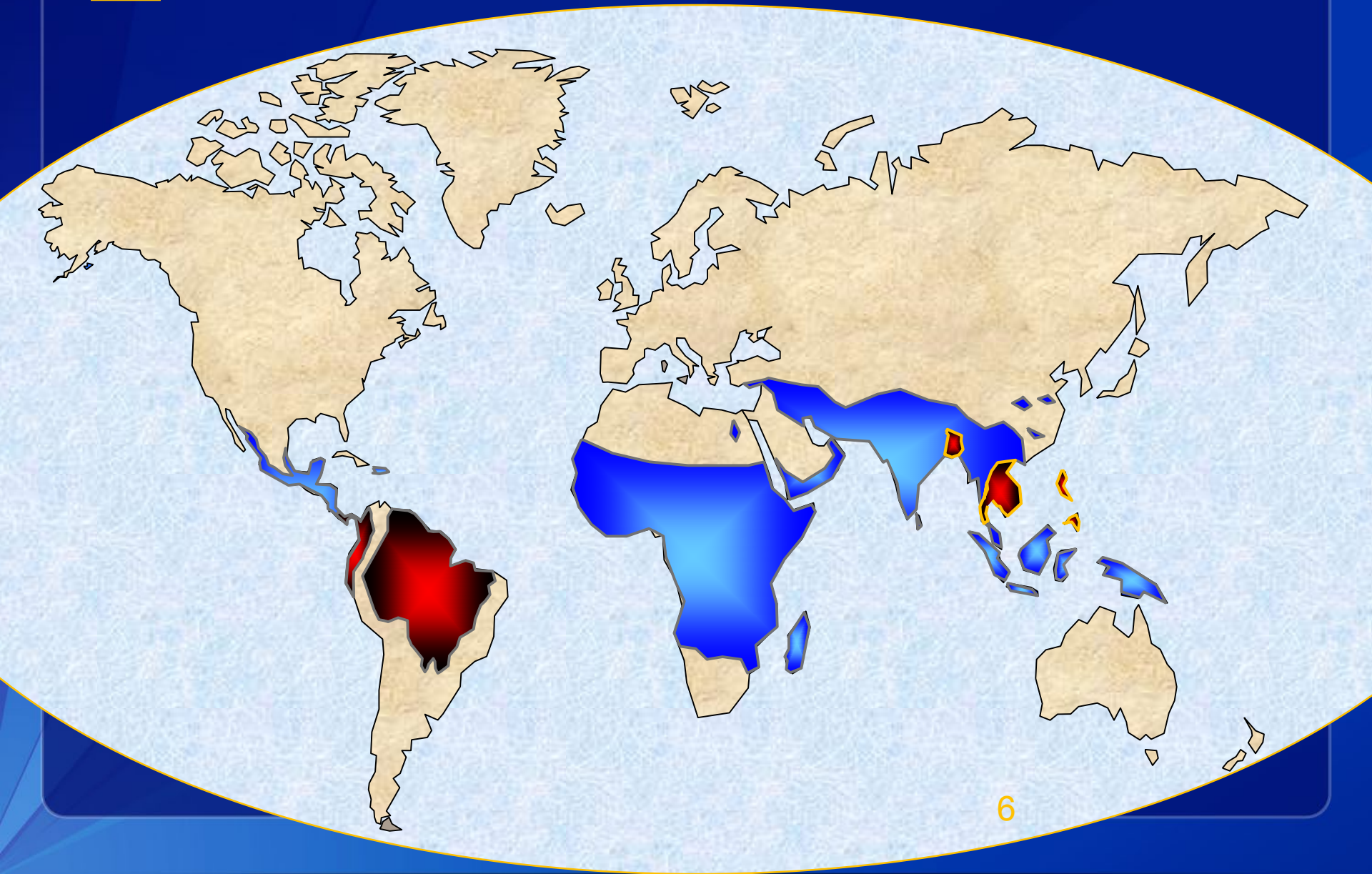
Distribution of Chloroquine Resistant *P. falciparum* circa 1960

Distribution of Malaria



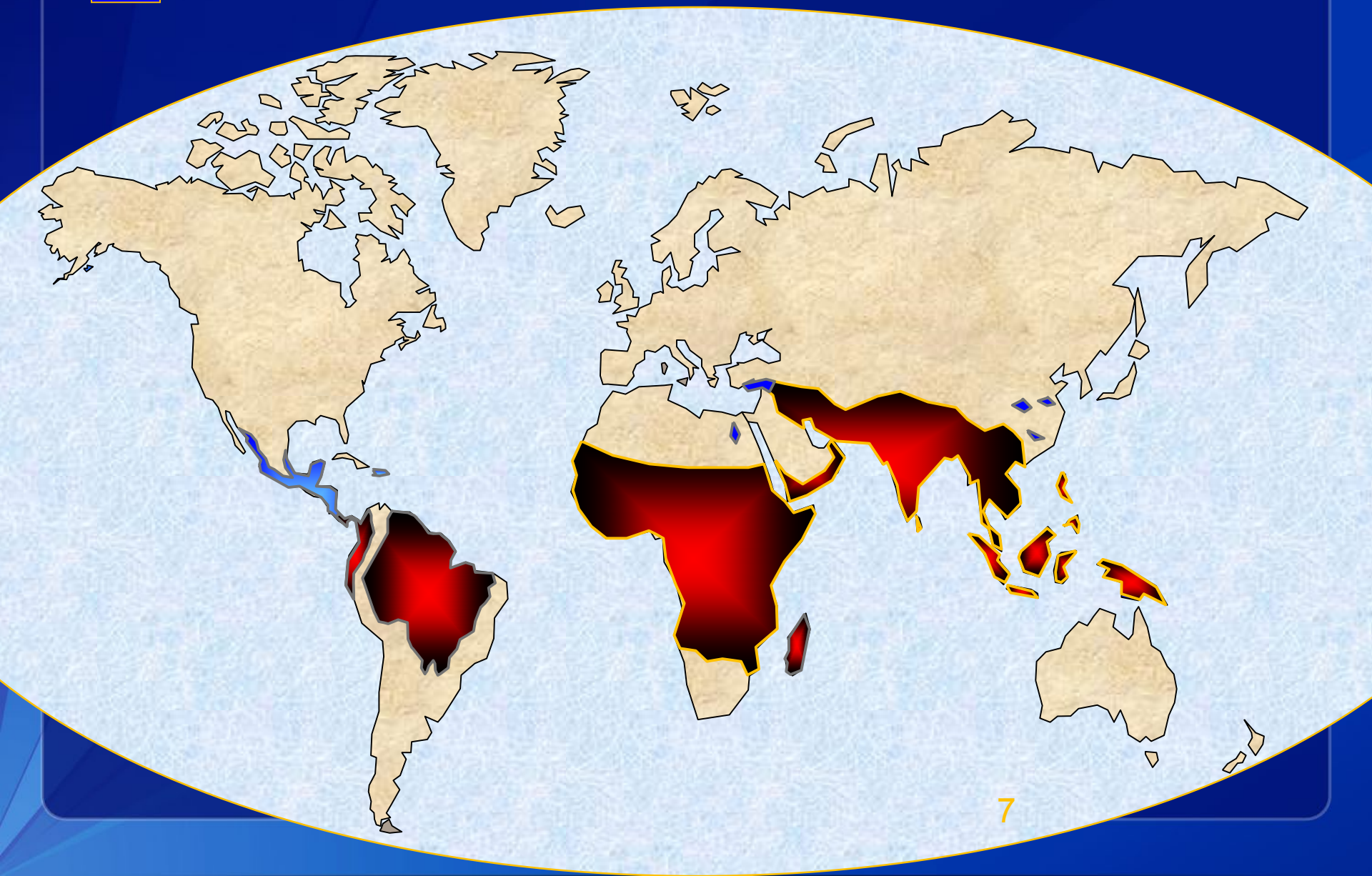
Distribution of Chloroquine Resistant *P. falciparum* circa 1970

Distribution of Malaria



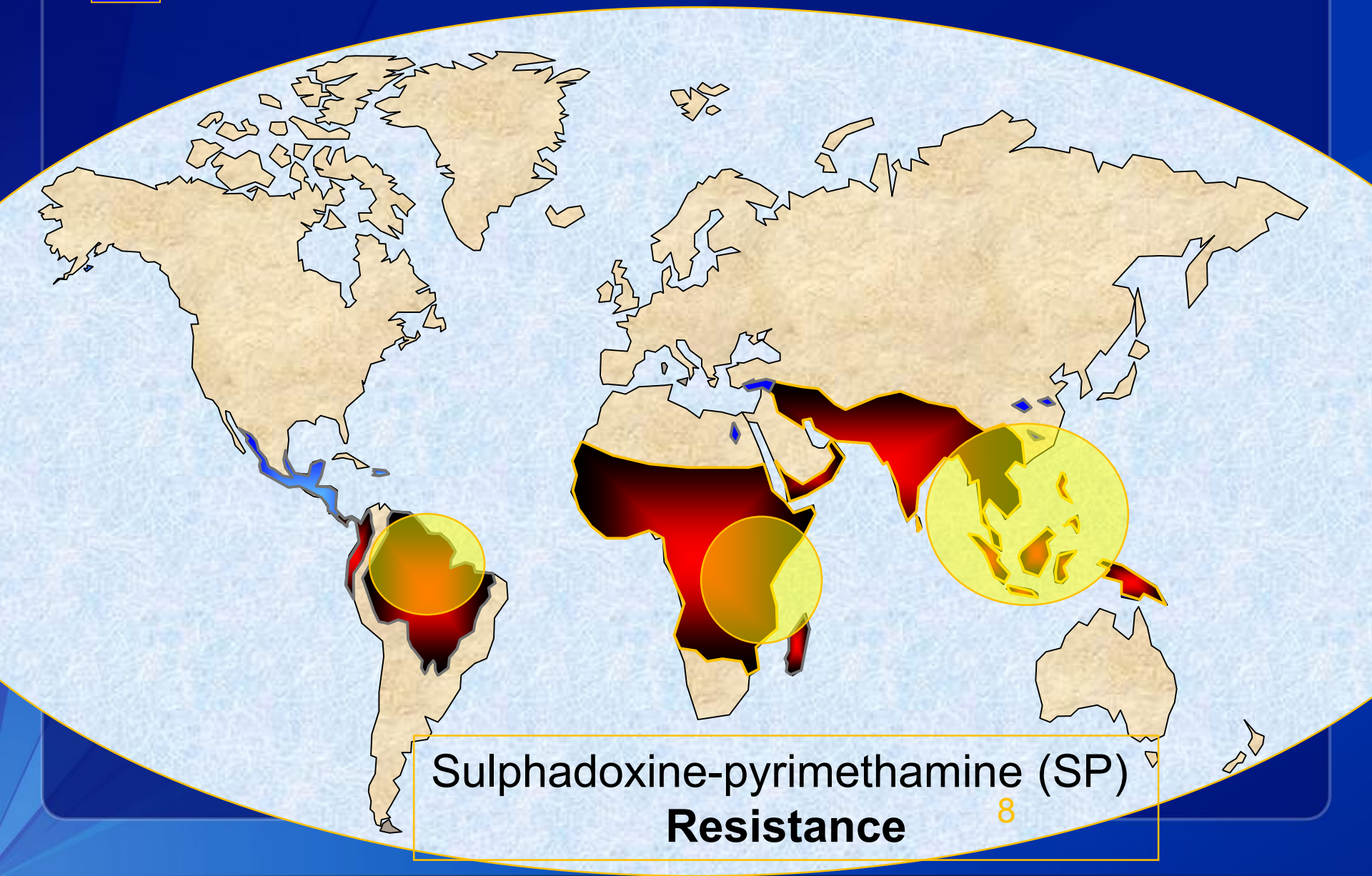
Distribution of Chloroquine Resistant *P. falciparum* circa 1980-present

Distribution of Malaria



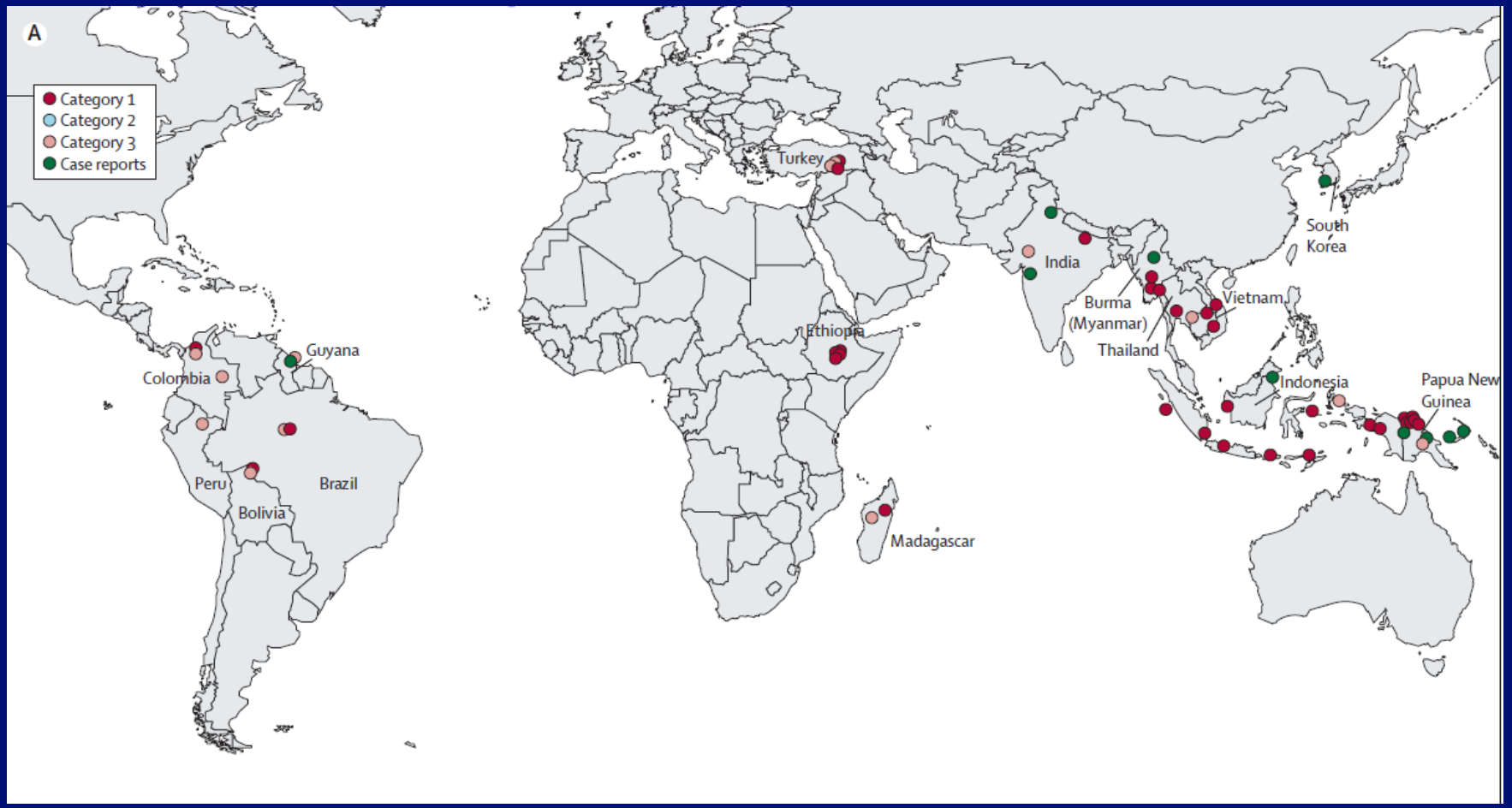
Distribution of Chloroquine Resistant *P. falciparum* circa 1990-2010

Distribution of Malaria



Sulphadoxine-pyrimethamine (SP)
Resistance

Chloroquine -resistant *P.vivax*



Category 1: >10% recurrences by day 28 irrespective of CQ levels
Category 2: recurrences with documented CQ level
Category 3: >5% recurrences by day 28 irrespective of CQ levels

How long does it take for anti -malarial resistance to develop?

Drug	Year Introduced	1st Resist. Reported	Difference (Years)
Quinine	1632	1910	278
Chloroquine *	1945	1957	12
Proguanil	1948	1949	1
SP*	1967	1967	0
Mefloquine *	1977	1982	5
Atovaquone	1996	1996	0
Artemisinin *	1994	2002	8

* *First occurred on the Thailand -Cambodia border*

THE LANCET Infectious Diseases Vol 2 April 2002

Gem mining, Thai-Cambodia border (1950s -1960s)

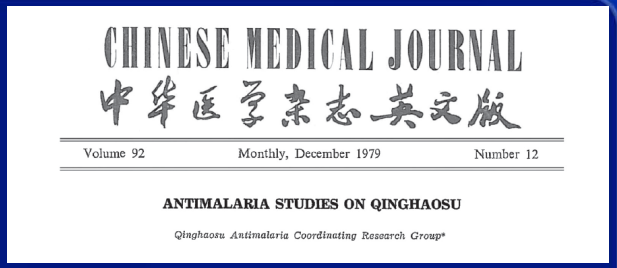
- Steady flow of newcomers from other regions of Cambodia and Thailand; in addition, miners from Vietnam, Myanmar, and Bangladesh
  - Many with low or no immunity
- Shafts created breeding sites for *Anopheles dirius*
  - Does not rest indoors→Hard to control with DDT
  - High breeding rate
- Miners slept outdoors or in rudimentary housing
- Chloroquine added to salt
  - Potential for subtherapeutic dosing
- Miners would return to home region

Pailin (Cambodia) today

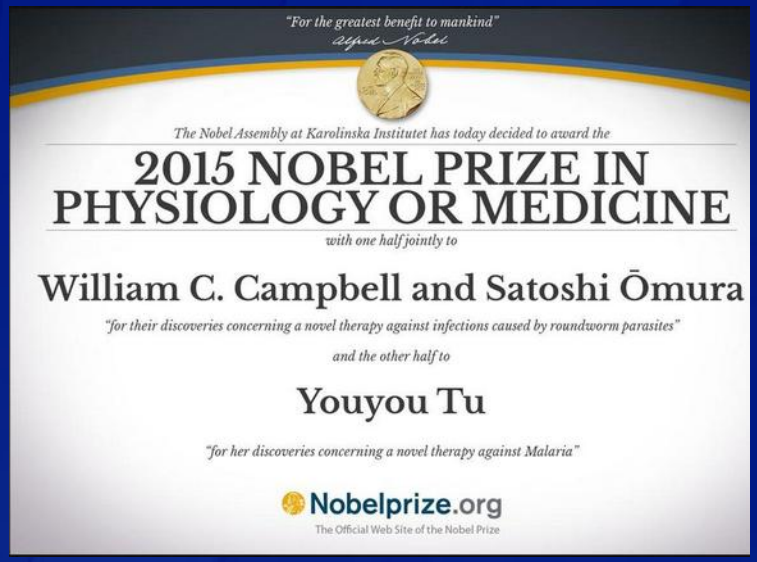
- Still a center of immigration and mining
- Poor health infrastructure
- Low quality antimalarials readily available
  - Counterfeit
  - Artemisinins without partner drug

Cambodia Times, June 11, 2014
http://www.cambodiadaily.com/news/scraping-out-a-living-in-pailins-spent-gem-mines-61043/

Artemisinins



- Qinghao : synonym for herbs of the *Artemisia* family
- 317-420 A.D: First role in treating fevers described
  - *A Handbook of Prescriptions for Emergencies* Ge Hong
- 1967: Office 523, Chinese malaria control agency coordinating antimalarial research
  - 2000 traditional Chinese medicines were considered
- 1971: initial success with Qinghao in rodents & primates
  - *Artemisiaannua* leaves
- 1972: human trials in Hainan and Beijing
- 1979: results reported in *Chinese Medical Journal*
- 1990s: Large scale trials

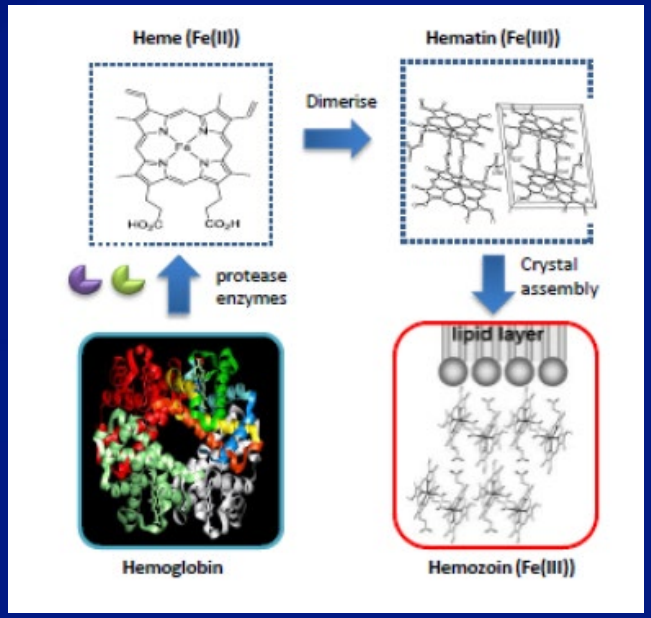

"For the greatest benefit to mankind"
Alfred Nobel
The Nobel Assembly at Karolinska Institutet has today decided to award the
2015 NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE
with one half jointly to
William C. Campbell and Satoshi Ōmura
"for their discoveries concerning a novel therapy against infections caused by roundworm parasites"
and the other half to
Youyou Tu
"for her discoveries concerning a novel therapy against Malaria"
Nobelprize.org
The Official Web Site of the Nobel Prize


应该把最完善的药
提供给世界人民

How do artemisinins work?
A few theories

- Interaction with intraparasitic heme*
  - Hematin: potentially toxic to parasite
  - Hemazoin (malaria pigment): non-toxic
- Calcium homeostasis interference
- Translationally controlled tumor protein (TCTP) homologue
  - Present in both tumor cells and plasmodia

*Thought to be most active during the trophozoite stage



Trends in Parasitology, September 2016, Vol. 32, No. 9

Molecules **2010**, *15*, 1705-1721; doi:10.3390/molecules15031705

Artemisinin Derivatives

- Safe and well-tolerated
- Rapidly effective (10,000 -fold reduction in 48 hours)
- In 2005, WHO recommended their use in all countries with endemic malaria
- Artesunate is the treatment of choice for severe malaria
- Artemisinin combination treatments (ACTs) are treatment of choice for uncomplicated malaria
  - Paired with another class in order to decrease chance of resistance

Trends in Parasitology, September 2016, Vol. 32, No. 9

Treating uncomplicated *P. falciparum* malaria

Treatment of uncomplicated P. falciparum malaria

Treat children and adults with uncomplicated *P. falciparum* malaria (except pregnant women in their first trimester) with one of the following recommended artemisinin-based combination therapies (ACT):

- artemether + lumefantrine
- artesunate + amodiaquine
- artesunate + mefloquine
- dihydroartemisinin + piperaquine
- artesunate + sulfadoxine–pyrimethamine (SP)

Strong recommendation, high-quality evidence

Duration of ACT treatment

ACT regimens should provide 3 days' treatment with an artemisinin derivative.
Strong recommendation, high-quality evidence

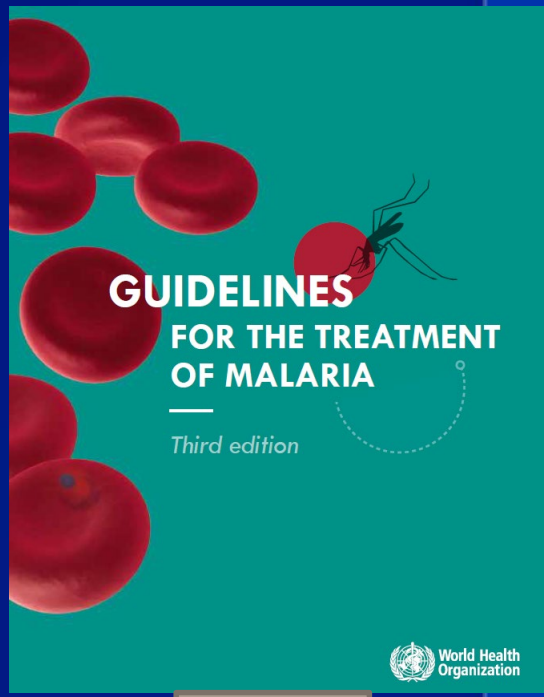
Artemisinin-containing compound (short-acting) + long-acting antimalarial

Genes associated with antimalarial resistance

K13: artemisinin

Pfmdr1: lumefantrine and mefloquine

DHFR and DHPS codons: SP



2015

Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial

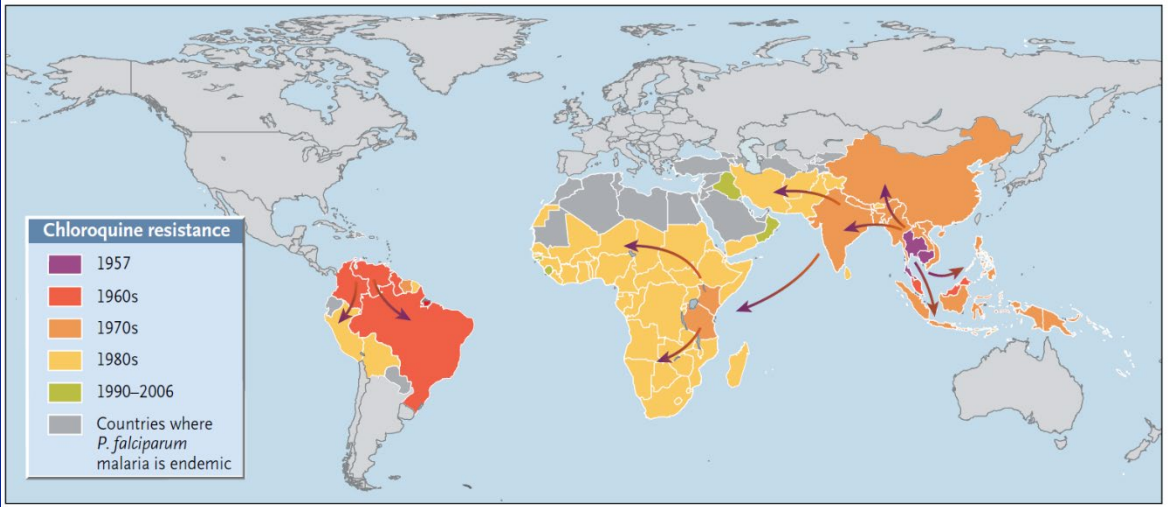
South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group*

www.thelancet.com Vol 366 August 27, 2005

Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial

www.thelancet.com Vol 376 November 13, 2010

Artemisinin Resistance



History of Chloroquine-Resistant *P. falciparum* Malaria.

- Is history repeating itself (e.g., chloroquine)?
- Artemisinin-based treatments: vital component of PMI's intervention strategy
- Treatment failures first described in Cambodia in 2008
  - PMI is actively tracking resistance in SE Asia
- Implications of spread to Africa

N ENGL J MED 371;5 NEJM.ORG JULY 31, 2014

ANTIMALARIAL DRUG RESISTANCE DEFINITIONS AND CONCEPTS

THERAPEUTIC EFFICACY – How well a drug works under optimal conditions: correct diagnosis, correct dose, directly observed treatment

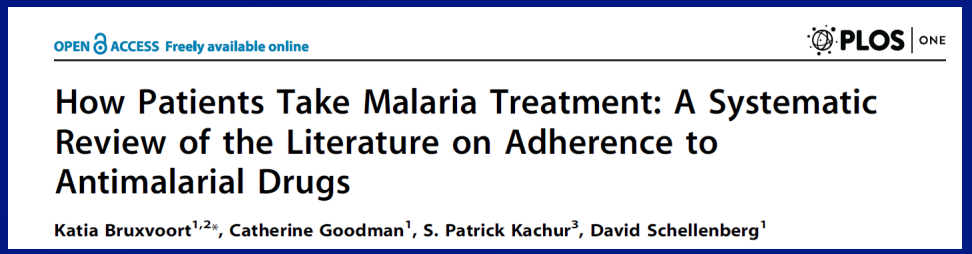
THERAPEUTIC EFFECTIVENESS – How well a drug works in real life – even assuming it is dispensed correctly, is the drug acceptable to the user, will it be taken in the proper amount for the correct length of time

Definition of Antimalarial Drug Resistance

Drug Resistance vs Treatment Failure

While Drug Resistance can cause Treatment Failure, not all Treatment Failure is due to Drug Resistance

- **Compliance**


OPEN ACCESS Freely available online

PLOS ONE

How Patients Take Malaria Treatment: A Systematic Review of the Literature on Adherence to Antimalarial Drugs

Katia Bruxvoort[1,2*], Catherine Goodman[1], S. Patrick Kachur[3], David Schellenberg[1]

Factors associated with adherence:

Higher education, older age, higher income, instructions received, more malaria knowledge

Factors a/w non-adherence:

Male, seeking care after 2 or more days, perception that illness not severe, different mother tongue than pharmacist

Definition of Antimalarial Drug Resistance

Drug Resistance vs Treatment Failure

- Compliance
- Wrong diagnosis
- **Absorption**

Review **Open Access**

The content of African diets is adequate to achieve optimal efficacy with fixed-dose artemether-lumefantrine: a review of the evidence

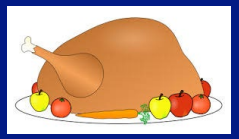
Zulfiqarali G Premji*[1], Salim Abdulla[2], Bernhards Ogutu[3], Alice Ndong[4], Catherine O Falade[5], Issaka Sagara[6], Nathan Mulure[7], Obiyo Nwaiwu[8] and Gilbert Kokwaro[9,10]

"Only a very small amount of dietary fat is necessary to ensure optima efficacy of AL and…the fat content of standard meals or breast milk in sub-Saharan Africa is adequate."

Artemether-lumefantrine

----------**DOSAGE AND ADMINISTRATION**----------

- Coartem Tablets should be taken with food. (2.1, 5.2)



Artesunate-amodiaquine

ARTESUNATE AMODIAQUINE WINTHROP should not be taken with a high-fat meal (see section "pharmacokinetic properties").

Dihydroartemisinin-piperaquine

Eurartesim with food and drink

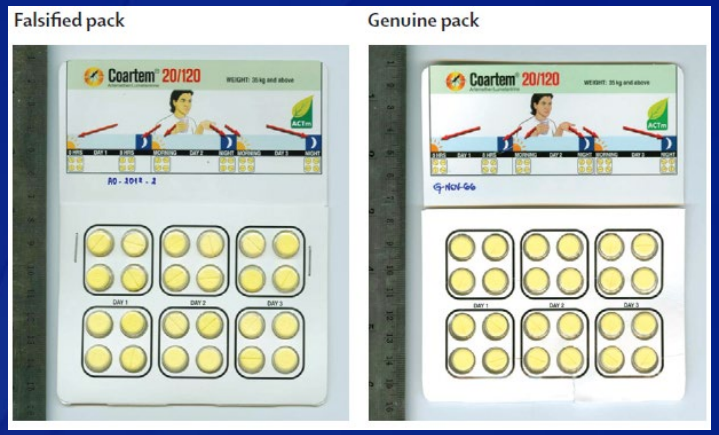
You should take the Eurartesim tablets with water only.

You should not take Eurartesim with grapefruit juice due to possible interactions.

Definition of Antimalarial Drug Resistance

Drug Resistance vs Treatment Failure

- Compliance
- Wrong diagnosis
- Absorption
- **Counterfeit or poor quality drug**



Multiple recent scandals, including one in Angola, involving **1.4 million** packets from China

Survey in Afghanistan found that **37%** of samples were sub-standard

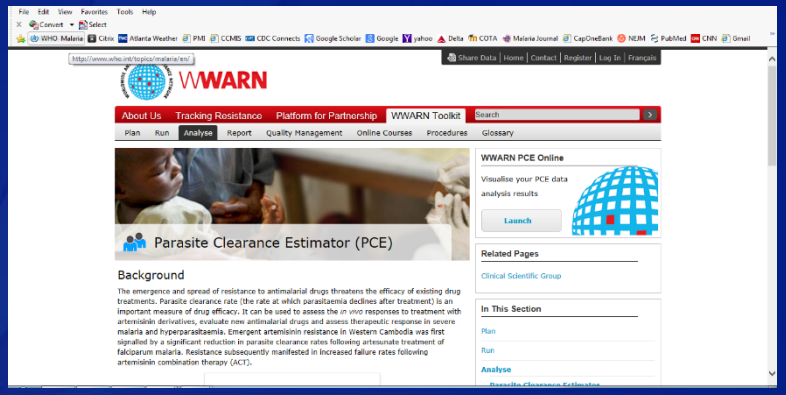
Newton, Lancet 2014
Lalani, AJTMH 2015

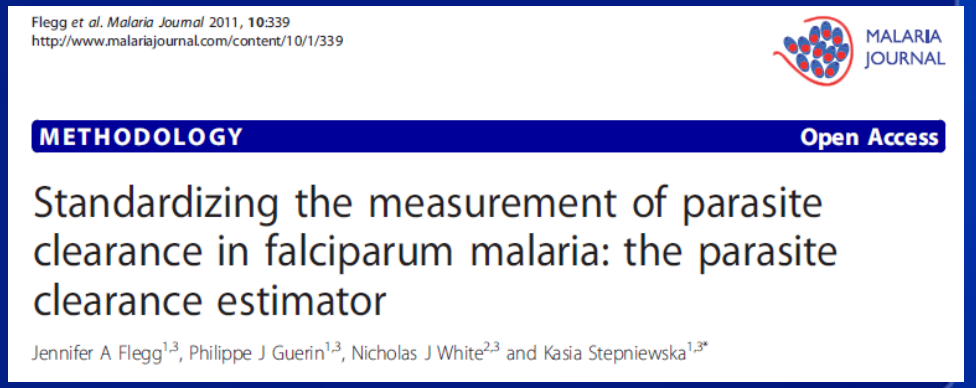
Specific Genetic Mutations Conferring Resistance

Quinine:	Pfmdr1
SP:	DHFR codons: 51, 59, 108, 164, DHPS codons: 436, 437, 540, 581, 613
Atovaquone:	cytochrome b
CQ:	PfCRT (cg2)
MQ:	PfMDR copy numbers
Artemisinin:	kelch propeller domain (k13)
Piperaquine:	plasmepsin 2 and 3 on chromosome 14

Parasite Clearance Time ($PCt_{1/2}$)

- Sensitive method of determining artemisinin resistance because of its rapid initial parasite clearance
- Affected by many factors
  - Better for groups of patients than individuals
- http://www.wwarn.org/





Delayed parasite clearance time

- Resistance associated with an average $PC_{1/2}$ > 5 hrs
  - Most still clear their infections
- In the Greater Mekong: high ACT failure rates mostly observed when concomitant resistance to partner drug exists
- Outside the Greater Mekong: treatment failure exists in the absence of artemisinin resistance; mainly due to partner drug resistance

Confirmed and Suspected Endemic Artemisinin Resistance

Suspected endemic artemisinin resistance:

Genotypic
- a prevalence ≥5% of infecting parasite strains carrying Kelch domain (k13) resistance-associated SNPs, **or**

Phenotypic
- a proportion ≥10% of patients still parasitemic on day 3 (72 hours ± 2) by microscopy **or**

Phenotypic
- ≥10% of patients with a half-life of the parasite clearance time ≥ 5 hours following treatment with ACT or artesunate monotherapy.

Need one of three

Confirmed and Suspected Endemic Artemisinin Resistance

Confirmed endemic artemisinin resistance:

Genotypic

- a prevalence ≥5% of infecting parasite strains carrying Kelch domain (k13) resistance-associated SNPs, **and**

Phenotypic

- all of the above (k13 mutated) patients still parasitemic on day 3 (72 hours ± 2) by microscopy **or**

Phenotypic

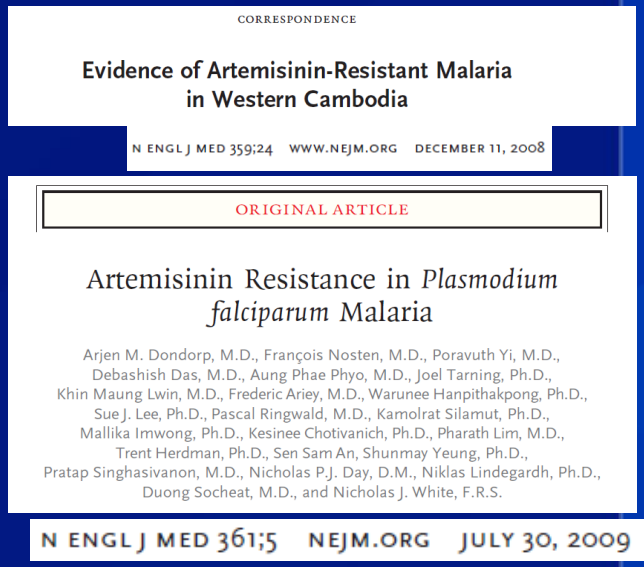
- all of the above (k13 mutated) patients with a half-life of the parasite clearance time ≥ 5 hours following treatment with ACT or artesunate monotherapy.

Need this + One of these two

RECENT LITERATURE AND DEVELOPMENTS IN ANTIMALARIAL RESISTANCE (2008-2018)

Western Cambodia again

- Noedl, 2008
  - 2 subjects with artemisinin resistance
  - 47.9% w/ parasitemia at 48 hours
- Dondorp, 2009
  - 6 of 20 failed w/ IV artesunate
  - Median clearance time: 84 hrs



CORRESPONDENCE

Evidence of Artemisinin-Resistant Malaria in Western Cambodia

N ENGL J MED 359;24 WWW.NEJM.ORG DECEMBER 11, 2008

ORIGINAL ARTICLE

Artemisinin Resistance in *Plasmodium falciparum* Malaria

Arjen M. Dondorp, M.D., François Nosten, M.D., Poravuth Yi, M.D., Debashish Das, M.D., Aung Phae Phyo, M.D., Joel Tarning, Ph.D., Khin Maung Lwin, M.D., Frederic Ariey, M.D., Warunee Hanpithakpong, Ph.D., Sue J. Lee, Ph.D., Pascal Ringwald, M.D., Kamolrat Silamut, Ph.D., Mallika Imwong, Ph.D., Kesinee Chotivanich, Ph.D., Pharath Lim, M.D., Trent Herdman, Ph.D., Sen Sam An, Shunmay Yeung, Ph.D., Pratap Singhasivanon, M.D., Nicholas P.J. Day, D.M., Niklas Lindegardh, Ph.D., Duong Socheat, M.D., and Nicholas J. White, F.R.S.

N ENGL J MED 361;5 NEJM.ORG JULY 30, 2009

Genome-wide studies

- SNPs were in non-coding region of chromosome, upstream of the genes that encode the DNA Pol
- kelch13 propeller SNPs a/w *in vivo* and *in vitro* resistance

A Major Genome Region Underlying Artemisinin Resistance in Malaria

Ian H. Cheeseman,[1] Becky A. Miller,[2] Shalini Nair,[1] Standwell Nkhoma,[1] Asako Tan,[2] John C. Tan,[2] Salma Al Saai,[1] Aung Pyae Phyo,[3] Carit Ler Moo,[3] Khin Maung Lwin,[3] Rose McGready,[3,4,5] Elizabeth Ashley,[3,4,5] Mallika Imwong,[4] Kasia Stepniewska,[4,5,7] Poravuth Yi,[8] Arjen M. Dondorp,[4,5] Mayfong Mayxay,[6] Paul N. Newton,[5,6] Nicholas J. White,[4,5] François Nosten,[3,4,5] Michael T. Ferdig,[2] Timothy J. C. Anderson[1]*

SCIENCE VOL 336 6 APRIL 2012

Genetic loci associated with delayed clearance of *Plasmodium falciparum* following artemisinin treatment in Southeast Asia

Shannon Takala-Harrison[a], Taane G. Clark[b,1], Christopher G. Jacob[a,1], Michael P. Cummings[c,2], Olivo Miotto[d,e,2], Arjen M. Dondorp[e], Mark M. Fukuda[f], Francois Nosten[e,g], Harald Noedl[h], Mallika Imwong[i], Delia Bethell[f], Youry Se[j], Chanthap Lon[i], Stuart D. Tyner[f], David L. Saunders[f], Duong Socheat[k], Frederic Ariey[l], Aung Pyae Phyo[e,g], Peter Starzengruber[h], Hans-Peter Fuehrer[h], Paul Swoboda[h], Kasia Stepniewska[m], Jennifer Flegg[m], Cesar Arze[n], Gustavo C. Cerqueira[n], Joana C. Silva[n], Stacy M. Ricklefs[o], Stephen F. Porcella[o], Robert M. Stephens[p], Matthew Adams[a], Leo J. Kenefic[a], Susana Campino[d,q], Sarah Auburn[q], Bronwyn MacInnis[d,q], Dominic P. Kwiatkowski[d,q], Xin-zhuan Su[r], Nicholas J. White[e], Pascal Ringwald[s], and Christopher V. Plowe[a,3]

240–245 | PNAS | January 2, 2013 | vol. 110 | no. 1

A molecular marker of artemisinin-resistant *Plasmodium falciparum* malaria

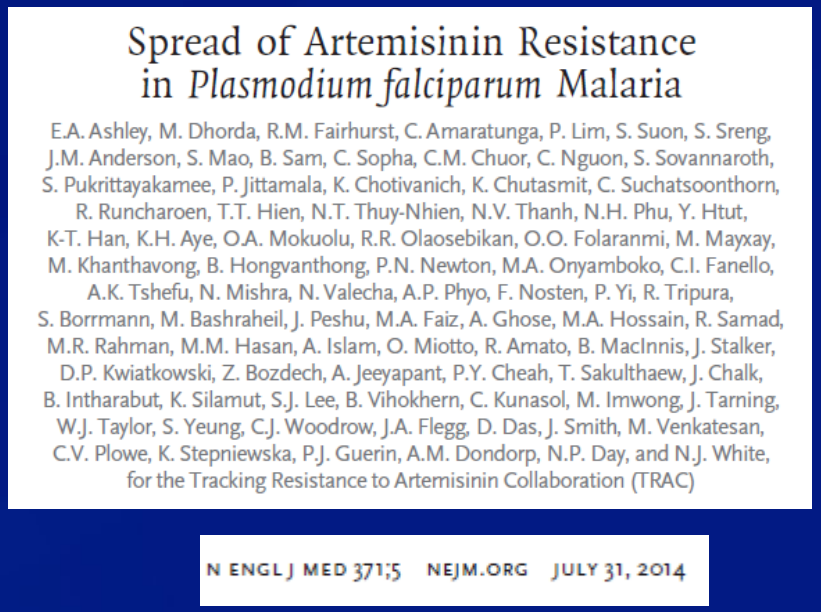
Frédéric Ariey[1,2]†, Benoit Witkowski[3], Chanaki Amaratunga[4], Johann Beghain[1,2]†, Anne-Claire Langlois[1,2], Nimol Khim[3], Saorin Kim[3], Valentine Duru[3], Christiane Bouchier[5], Laurence Ma[5], Pharath Lim[3,4,6], Rithea Leang[6], Socheat Duong[6], Sokunthea Sreng[6], Seila Suon[6], Char Meng Chuor[6], Denis Mey Bout[7], Sandie Ménard[8]†, William O. Rogers[9], Blaise Genton[10], Thierry Fandeur[1,3], Olivo Miotto[11,12,13], Pascal Ringwald[14], Jacques Le Bras[15], Antoine Berry[8]†, Jean-Christophe Barale[1,2]†, Rick M. Fairhurst[4]*, Françoise Benoit-Vical[16,17]*, Odile Mercereau-Puijalon[1,2]* & Didier Ménard[3]*

50 | NATURE | VOL 505 | 2 JANUARY 2014

Ashley, NEJM 2014

- 1241 subjects, 10 countries, and 15 sites
- Subjects received oral artesunate followed by an ACT *
- High degree of detectable parasitemia at 72 hours in Thailand and Cambodia

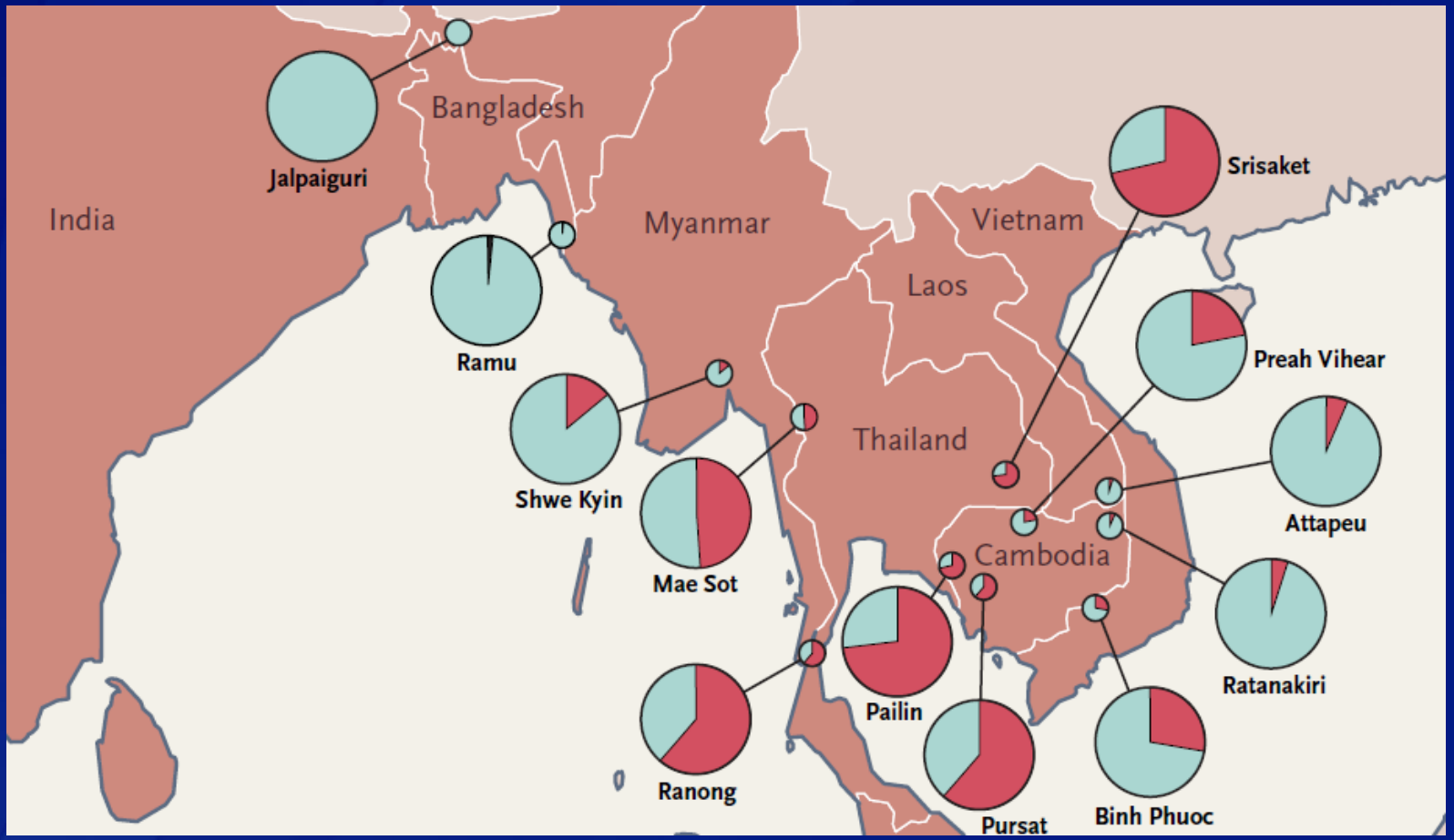
*slight variations existed in dosing regimen from country to country



Spread of Artemisinin Resistance in *Plasmodium falciparum* Malaria

E.A. Ashley, M. Dhorda, R.M. Fairhurst, C. Amaratunga, P. Lim, S. Suon, S. Sreng, J.M. Anderson, S. Mao, B. Sam, C. Sopha, C.M. Chuor, C. Nguon, S. Sovannaroth, S. Pukrittayakamee, P. Jittamala, K. Chotivanich, K. Chutasmit, C. Suchatsoonthorn, R. Runcharoen, T.T. Hien, N.T. Thuy-Nhien, N.V. Thanh, N.H. Phu, Y. Htut, K-T. Han, K.H. Aye, O.A. Mokuolu, R.R. Olaosebikan, O.O. Folaranmi, M. Mayxay, M. Khanthavong, B. Hongvanthong, P.N. Newton, M.A. Onyamboko, C.I. Fanello, A.K. Tshefu, N. Mishra, N. Valecha, A.P. Phyo, F. Nosten, P. Yi, R. Tripura, S. Borrmann, M. Bashraheil, J. Peshu, M.A. Faiz, A. Ghose, M.A. Hossain, R. Samad, M.R. Rahman, M.M. Hasan, A. Islam, O. Miotto, R. Amato, B. MacInnis, J. Stalker, D.P. Kwiatkowski, Z. Bozdech, A. Jeeyapant, P.Y. Cheah, T. Sakulthaew, J. Chalk, B. Intharabut, K. Silamut, S.J. Lee, B. Vihokhern, C. Kunasol, M. Imwong, J. Tarning, W.J. Taylor, S. Yeung, C.J. Woodrow, J.A. Flegg, D. Das, J. Smith, M. Venkatesan, C.V. Plowe, K. Stepniewska, P.J. Guerin, A.M. Dondorp, N.P. Day, and N.J. White, for the Tracking Resistance to Artemisinin Collaboration (TRAC)

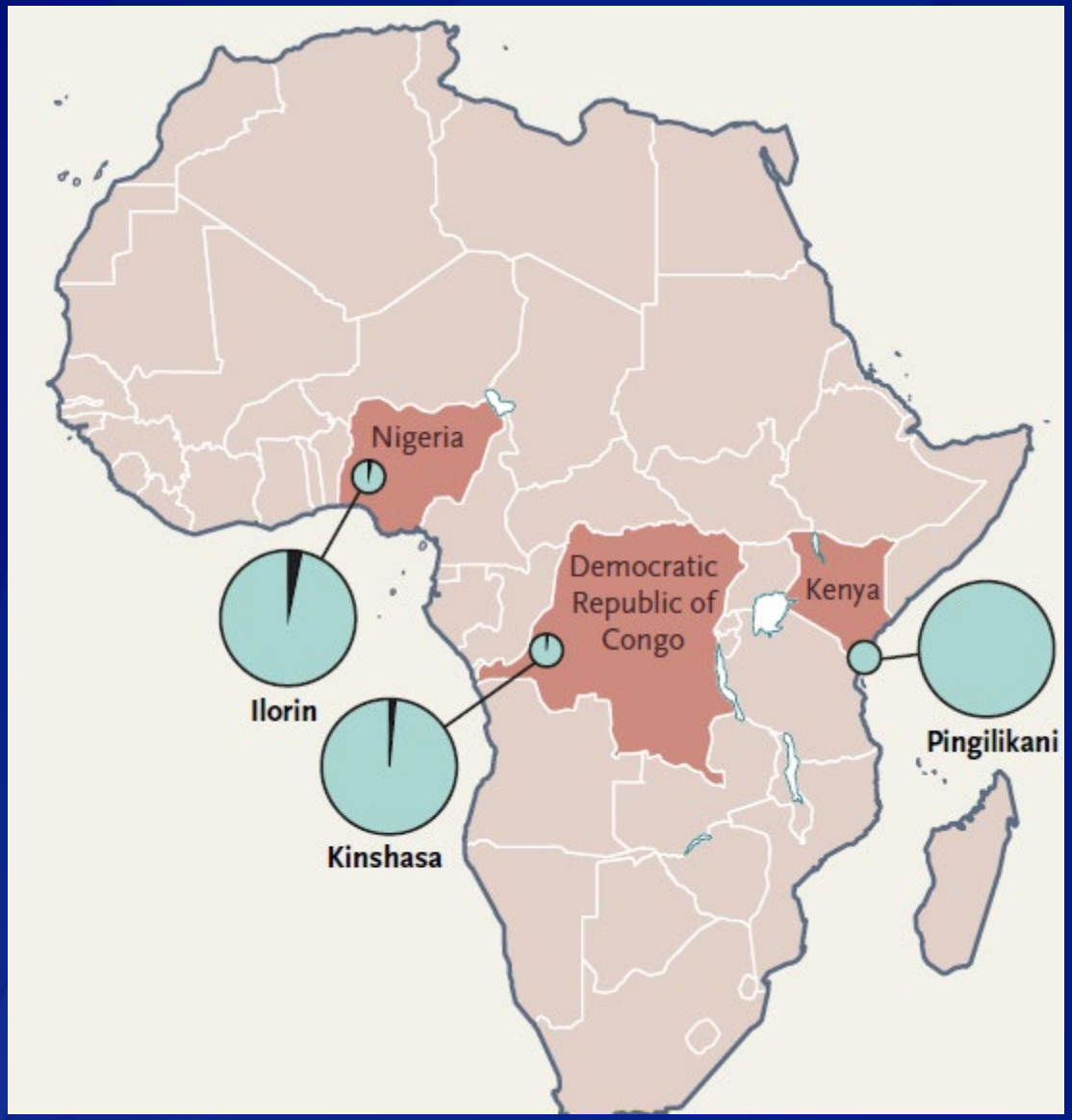
N ENGL J MED 371;5 NEJM.ORG JULY 31, 2014



Parasite clearance half-life ≤5 hr

Parasite clearance half-life >5 hr, *kelch13* polymorphisms at or beyond amino acid position 441

Parasite clearance half-life >5 hr, no *kelch13* polymorphisms at or beyond amino acid position 441


Nigeria
Democratic Republic of Congo
Kenya
Ilorin
Kinshasa
Pingilikani
Parasite clearance half-life ≤5 hr
Parasite clearance half-life >5 hr, kelch13 polymorphisms at or beyond amino acid position 441
Parasite clearance half-life >5 hr, no kelch13 polymorphisms at or beyond amino acid position 441

Cambodia Lao PDR Vietnam	China Myanmar Thailand	Africa

TABLE 1

Canditate and validated K13 resistance mutations*

K13 MUTATION	CLASSIFICATION
E252Q	*Not associated*
P441L	Candidate
F446I	Candidate
G449A	Candidate
N458Y	**Validated**
Y493H	**Validated**
G538V	Candidate
R539T	**Validated**
I543T	**Validated**
P553L	Candidate
R561H	**Validated**
V568G	Candidate
P574L	Candidate
A578S	*Not associated*
C580Y	**Validated**
A675V	Candidate

* Other less frequent variants have been associated with in vivo or in vitro tests, or both: M476I; C469Y; C469F; M476I; K479I; A481V; R515K; S522C; P527L; N537I; N537D; G538V; R575K; M579I; D584V; P667T; F673I; H719N.

- In SE Asia, distinct alleles originating from multiple independent events of emergence have been observed
- In Africa, non-synonymous mutations are rare and diverse

World Health Organization

CASE REPORT Open Access

Poor response to artesunate treatment in two patients with severe malaria on the Thai–Myanmar border

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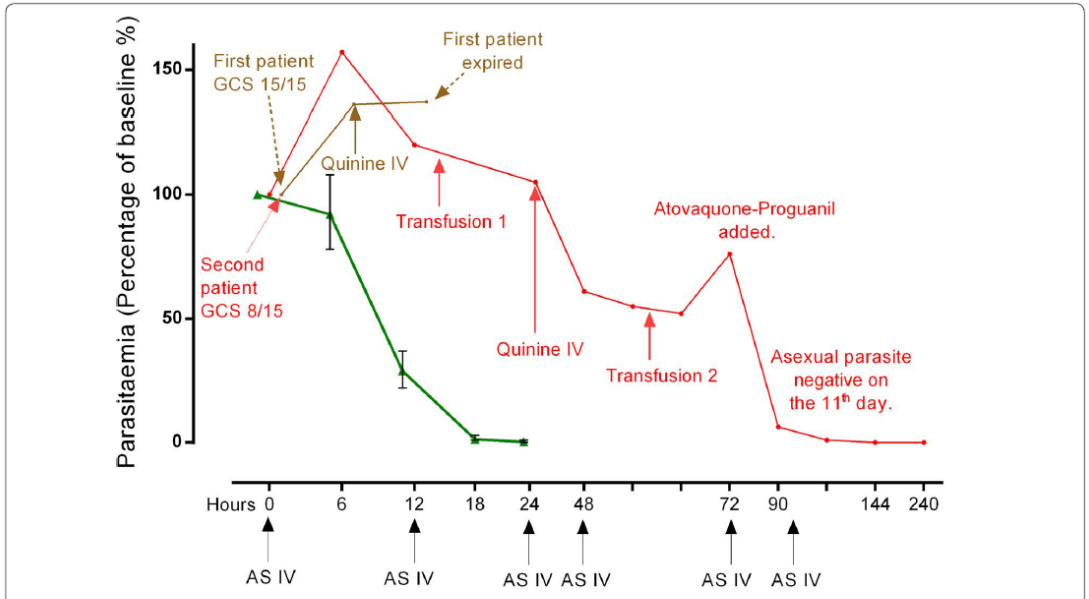
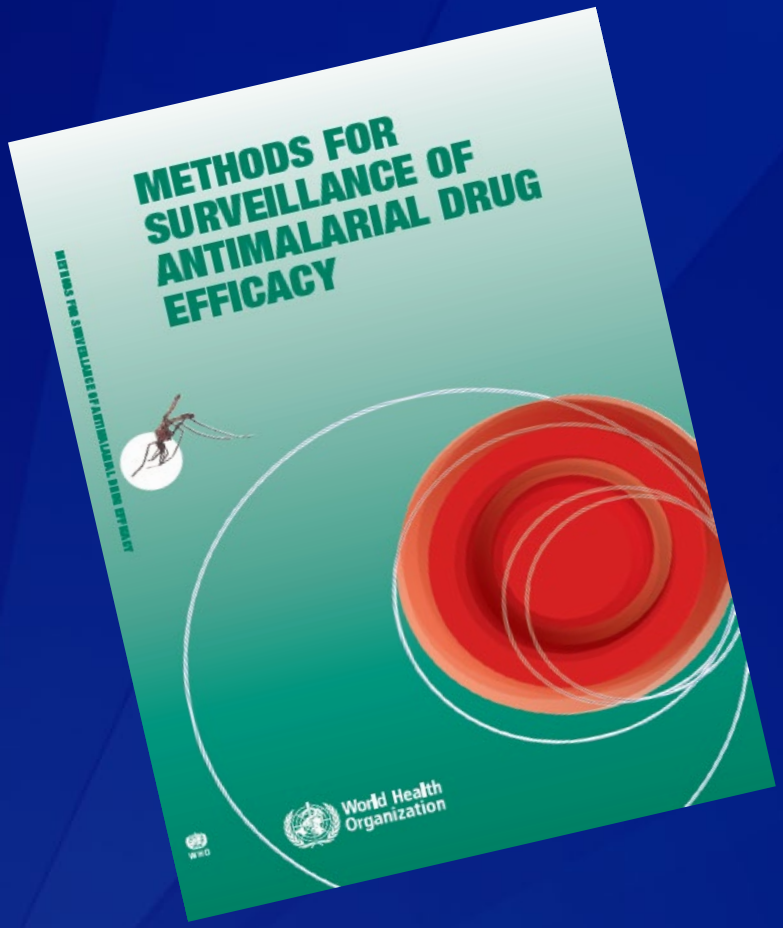


Fig. 1 Clinical and parasitological response of two severe malaria cases compared to those patients with uncomplicated hyperparasitaemia who received artesunate per oral (green) (median: IQR)

MONITORING DRUG RESISTANCE

Monitoring Antimalarial Drug Resistance



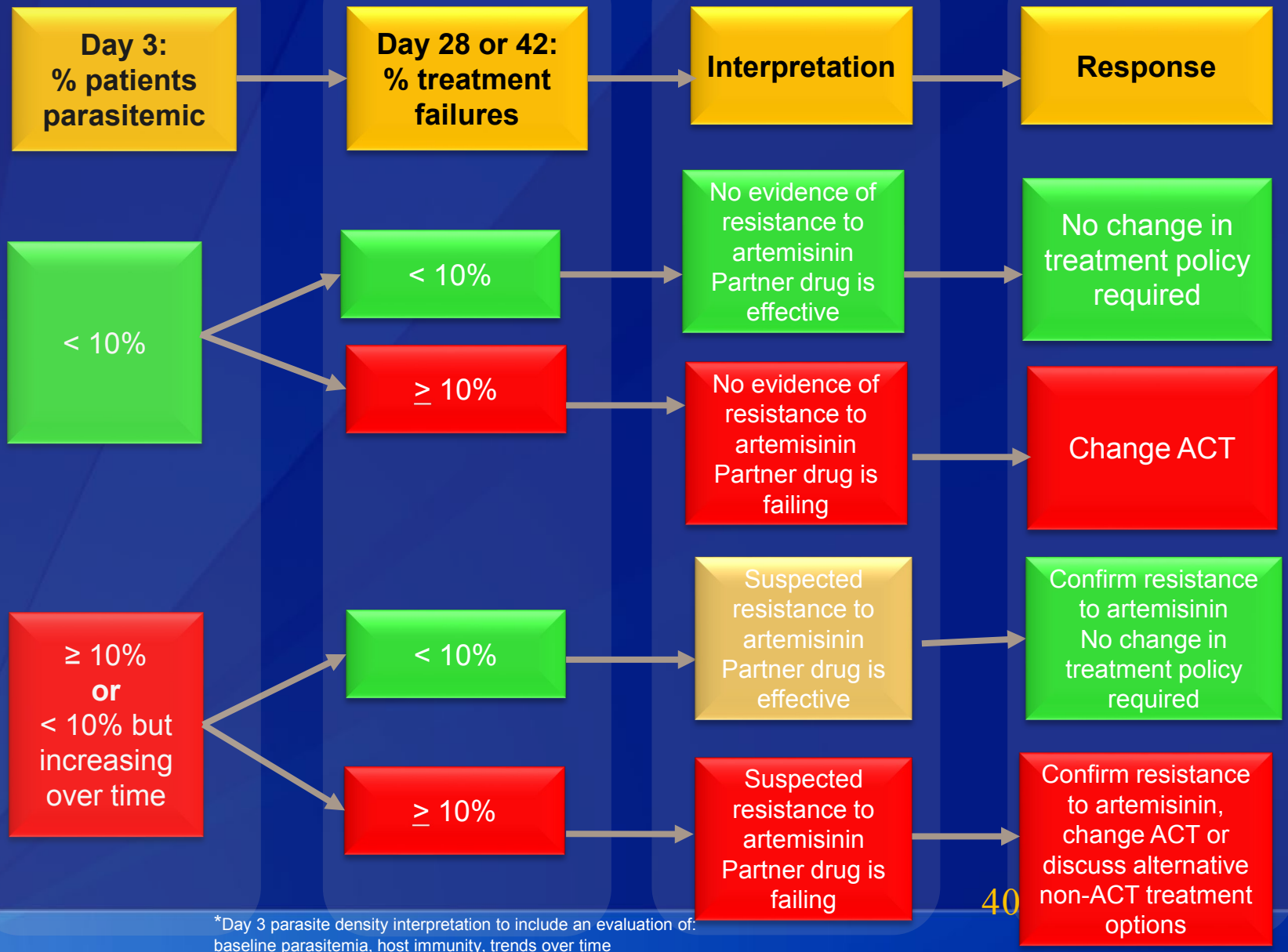
- Establishment of 4 to 8 sites in each country
- 1st and 2nd line antimalarial medicines should be evaluated at least once every 24 months in all countries with *P. falciparum*
- All studies must be accompanied by molecular assessment (e.g., PCR) to assist in distinguishing recrudescence from re-infections
- All studies must be conducted in accordance with the WHO testing protocol

Appendix 6. SCHEDULE OF FOLLOW-UP ACTIVITIES

	Day										
	0	1	2	3	7	14	21	28	35	42	Any other
Procedure											
Clinical assessment	X	X	X	X	X	X	X	X	(X)	(X)	(X)
Temperature	X	X	X	X	X	X	X	X	(X)	(X)	(X)
Blood slide for parasite count	X		X	X	X	X	X	X	(X)	(X)	(X)
Urine sample	(X)										
Blood for:											
genotyping	X				X	X	X	X	(X)	(X)	X
haemoglobin or haematocrit	(X)					(X)		(X)		(X)	(X)
molecular markers	(X)				(X)	(X)	(X)	(X)	(X)	(X)	(X)
in vitro test	(X)										
antimalarial blood concentration	(X)				(X)	(X)	(X)	(X)	(X)	(X)	(X)
Treatment											
Medicine to be tested	X	(X)	(X)								
Rescue treatment		(X)	(X)	(X)	(X)	(X)	(X)	(X)			(X)

Parentheses denote conditional or optional activities. For example, treatment would be given on days 1 and 2 only for 3-day dosing. On day 1, the patient should be examined for parasitaemia if he or she has any danger signs. Rescue treatment could be given on any day, provided that the patient meets the criteria for treatment failure. Extra days are any days other than regularly scheduled follow-up days when the patient returns to the facility because of recurrence of symptoms. On extra days, blood slides may be taken routinely or at the request of the clinical staff.

Decision making forTESs



*Day 3 parasite density interpretation to include an evaluation of: baseline parasitemia, host immunity, trends over time

Important TES vocabulary

METHODS FOR SURVEILLANCE OF ANTIMALARIAL DRUG EFFICACY

Classification of responses to treatment

The same definitions of treatment response are now used for all levels of malaria transmission:

Early treatment failure (ETF)

- danger signs or severe malaria on day 1, 2 or 3, in the presence of parasitaemia;
- parasitaemia on day 2 higher than on day 0, irrespective of axillary temperature;
- parasitaemia on day 3 with axillary temperature ≥ 37.5 °C; and
- parasitaemia on day 3 ≥ 25% of count on day 0.

Late clinical failure (LCF)

- danger signs or severe malaria in the presence of parasitaemia on any day between day 4 and day 28 (day 42) in patients who did not previously meet any of the criteria of early treatment failure; and
- presence of parasitaemia on any day between day 4 and day 28 (day 42) with axillary temperature ≥ 37.5 °C in patients who did not previously meet any of the criteria of early treatment failure.

Late parasitological failure (LPF)

- presence of parasitaemia on any day between day 7 and day 28 (day 42) with axillary temperature < 37.5 °C in patients who did not previously meet any of the criteria of early treatment failure or late clinical failure.

Adequate clinical and parasitological response (ACPR)

- absence of parasitaemia on day 28 (day 42), irrespective of axillary temperature, in patients who did not previously meet any of the criteria of early treatment failure, late clinical failure or late parasitological failure.

Data interpretation and policy considerations

Once the data have been validated, the national coordination team should forward its recommendations to drug policy-makers for action. A group of experts (with representatives of the national malaria control programme, Ministry of Health, universities, research institutes, national reference laboratory) should be established to review the data. WHO guidelines for the treatment of malaria recommend that first-line treatment should be changed if the total failure rate exceeds 10%; however, efficacy and failure rates should be considered in the context of their 95% confidence intervals. A decline in efficacy can be due to a number of factors, which should be addressed in confirmatory studies of pharmacokinetics and in vitro and molecular studies. It is likely that the results will differ by site: some may have a substantial deterioration in treatment efficacy, while others may

▶ If failure occurs after D7, PCR is mandatory in areas of both high and low-to-moderate transmission, to distinguish between reinfection and recrudescence, to confirm the *Plasmodium* species or to detect mixed infection. Therefore, failure with a species other than *P. falciparum* should also be confirmed by PCR.

- Reinfection
- Recrudescence
- PCR corrected

Efficacy of Artemether-Lumefantrine and Dihydroartemisinin-Piperaquine for Treatment of Uncomplicated Malaria in Children in Zaire and Uíge Provinces, Angola

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TABLE 3 Response to treatment in therapeutic efficacy studies in Zaire and Uíge Provinces, Angola, in 2013

Parameter	Result in study arm			
	AL		DP	
	Zaire (n = 79)	Uíge (n = 78)	Zaire (n = 80)	Uíge (n = 83)
ACPR, n (%)	61 (77)	72 (92)	79 (99)	83 (100)
Treatment failure, n (%)	18 (23)	6 (7.7)	1 (1.2)	0 (0)
Early	1 (1.3)	0 (0)	0 (0)	0 (0)
Late	17 (22)	6 (7.7)	1 (1.2)	0 (0)
Day 14	1 (1.3)	0 (0)	0 (0)	0 (0)
Day 21	10 (13)	3 (3.8)	0 (0)	0 (0)
Day 28	6 (7.6)	3 (3.8)	1 (1.2)	0 (0)
Reinfections	10 (13)	4 (5.1)	1 (1.2)	0 (0)
Recrudescence	7 (8.9)	2 (2.6)	0 (0)	0 (0)
Day 3 clearance, % (95% CI)	100 (96–100)	97.6 (92–100)	100 (96–100)	100 (96–100)
Cumulative success rate on day 28, % (95% CI)				
PCR uncorrected	77.4 (69–87)	92.3 (87–98)	98.8 (96–100)	100[a]
PCR corrected	89.6 (83–97)	97.4 (94–100)	100[a]	100[a]
Proportion of ACPR on day 28, % (95% CI)				
PCR uncorrected	77.2 (66–86)	92.3 (84–97)	98.8 (93–100)	100 (96–100)
PCR corrected	88.4 (78–95)	97.3 (91–100)	100 (95–100)	100 (96–100)

[a] Confidence intervals were not calculated for the Kaplan-Meier estimator when the rate was 100%.

K13 (artemisinin): all wild type

Pfmdr1 (lumefantrine): single copy number, haplotypes c/w resistance (NFD, NYD)